Naval Med. Res. Inst.

UNPUBLISHED PRELIMINARY DATA

Basic Physiological Mechanisms which Defend the Human Body against Heat and Cold and the Extent and Efficiency of Energy Transformations in the Human Body and in Isolated Body Constituents at the Molecular Level

QUARTERLY REPORT ON RESEARCH CONTRACT #R-38 WITH NASA, COVERING PERIOD JULY-AUGUST-SEPTEMBER 1963

Quarterly Report July-Sept 1963

7p

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I. HUMAN ENERGETICS - (NASA Order R-38) (NASA CR-52183)

[redacted]

(1) TEMPERATURE-REGULATION:

Measurements performed under the contract, combined with Nakayama's findings on single neurons in the hypothalamus of the cat and Hensel's findings on cold-receptors of the human skin permit a tentative comparison between

(a) The intensity of total thermal stimulation

(b) The firing rates of the sensory neurons involved, and

(c) The resulting intensity of the thermoregulatory responses as shown and explained in the figure-table, enclosure (1).

(2) LECTURE:

An invited lecture, "The Thermal Homeostasis of Man" was delivered on September 10, 1963 at Cambridge, England, in the "Symposium on Homeostasis and Feedback Mechanisms" of the Society for Experimental Biology by T. H. Benzinger.

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(3) INTERNATIONAL USES OF GRADIENT LAYER CALORIMETRY:

At the Symposium in Cambridge and at the International Meeting on Bio-Meteorology in Pau (Pyrennées, France) the potential of the method of "gradient layer-calorimetry" (Bio-Energetics Laboratories) in the life sciences was widely discussed. A project of a gradient layer calorimeter large enough for cattle at the Hannah Dairy Institute, Ayr, Scotland, has been funded with 15,000 Pound Sterling. Other projects are underway in Australia, in Canada and at Liverpool, England.

II. MOLECULAR ENERGETICS

(1) CHAIRMANSHIP:

T. H. Benzinger acted as chairman of Session V, "Biochemical Thermodynamics" at the "Symposium on Thermodynamics and Thermochemistry" in Lund, Sweden, July 18-23, 1963, held in connection with the meetings of the "International Union of Pure and Applied Chemistry" in England.

(2) CHEMOSYNTHESIS: (PRINCIPAL INVESTIGATOR: LUTZ KIESOW)

During the present report-period the reversal of the energy transforming step in nitrobacter chemosynthesis has been observed:

$$(1)\quad DPN.H_2 + NO_3^- \longrightarrow DPN + NO_2^- + H_2O$$

The reaction proceeds in cell-free extracts as well as in the intact organism. It does not require molecular oxygen. It is thermodynamically feasible without an energy-donating, coupled reaction. The identification in nitrobacter, of reaction (1) -- a reversal of the chemosynthetic process of energy capture -- has removed a serious obstacle to further attempts at clarifying the mechanisms of "biosynthesis without light." It was decisively important for the following reasons:

(a) Reaction (1), a reversal of nitrite-oxidation, interfered with, and obscured the observation of the main reaction under study, in which the inorganic energy is harnessed in a biochemical compound, namely the process of the following "net" formulation:

$$(2)\ \mathrm{DPN} + \mathrm{NO_2^-} + \mathrm{H_2O} \longrightarrow \mathrm{DPN.H2} + \mathrm{NO_3^-}$$

Reaction (2) proceeds only in the presence of molecular oxygen and is not thermodynamically feasible as written in net formulation.

(b) Reaction (1) which <u>is</u> thermodynamically feasible without another, driving, reaction, will permit to measure directly, thermodynamic quantities and additional energy-requirements, of net reaction (2), the energy-transforming step in nitrobacter-chemosynthesis (the "chemolysis" of water with formation of $\mathrm{DPN.H_2}$).

(c) With the recognition and elimination of reaction (1) in nitrobacter it has been established beyond doubt by stoichiometric proof, that reduced pyridine-nucleotide is the product of the energy-transforming step in the process of primeval biosynthesis. Until then (see progress reports dated April 30 and July 31, 1963) this fact had been concluded indirectly, from the identical kinetics of nitrite-oxidation and pyridine nucleotide-reduction in our experiments.

(d) The special biological importance of the presence of an enzyme, catalyzing reaction (1) in nitrobacter is apparent:

When circumstances such as scarcity of carbon dioxide prevent assimilation and growth, the precious sources of energy in soil-nitrite are not wasted in continued oxidation. They may instead be replenished by enzymic production of NO_2^- from perishable organic sources, for later utilization under favorable conditions.

In summary, a central and now well established finding made under this project is the energy-transforming step, in which water is "chemolyzed" -- (not dissociated) - and DPN.H_2, energy-donor of the life process, is formed. It may be noted, that for "photo"-synthesis this state of the art has not yet been attained.

From the findings described above the thermodynamics of "biosynthesis without light" may now be developed using instrumentation and experiences not available at any other laboratory, nationally nor internationally. This illustrates the importance of continued and permanent collaboration in one laboratory between the two investigators representing two different fields, Bio-Energetics and Biochemistry. The collaboration is essential for all aspects of Contract #R-38 and specifically, for the two projects, "Chemosynthesis" and "Metabolic and Immunologic Characteristics of Cells."

Twenty-five copies of the publication by Lutz Kiesow entitled, "The Energy-Transforming Step in Nitrobacter-Chemosynthesis" (see quarterly report covering period April-May-June 1963) will be mailed under separate cover.

TEMPERATURE STIMULI, THERMORECEPTOR-FIRING RATES, AND REGULATORY RESPONSES IN HEAT-LOSS OR HEAT PRODUCTION

Figures are presented for a standard-response of 20 cal/sec, a 100% increase of basal human heat production (+) or heat loss (-) as shown in the last column at right. The first column of figures gives in °C the increase (+) or decrease (-) of temperature at the site of reception, required as a stimulus to produce the standard-response, 20 cal/sec. The middle column of figures gives single-neuron firing-rates (always an increase, +) resulting from the stimulus as tabulated and required to produce the standard-response.

Figures for skin cold-receptor firing-rates are quoted from Hensel and Boman, (experiments on man), and for pre-optic neurons, from T. Nakayama (experiments on cats). To produce the cold-responses as tabulated, the entire skin area, except the head must be exposed to the stimulus.

In their power to respond with increased firing-rate to changes in temperature-level, the hypothalamic warm-sensor neurons are 16 times superior to the cold-receptors of the skin. On the other hand, in their power of response to a given firing rate per single sensory neuron, the inhibition of sweating from the skin is the most powerful of the effector mechanisms. It requires only 12 impulses per minute to elicit the standard response. Central elicitation of sweating and central inhibition of metabolic rate are second (each 50 impulses per minute) and the metabolic drive from the skin comes third (120 impulses per minute required to elicit the standard response of 20 cal/sec).

It may be noteworthy, that firing rates of skin cold-receptors have ten times more power when inhibiting a function (sweating) than they have when driving a function (metabolic heat production). Similarly, at the central sensor, warm-inhibition (of metabolic heat production) arises first, at temperatures far below the setpoint. The drive (for sweating) begins first at the setpoint and continues with further increasing temperature. Possibly the relation between inhibiting and driving strength explains the dual nature of the setpoint, at the vortex between the chemical and physical regulations of body temperature: The inhibiting function begins early. It becomes complete at the same stimulus-intensity, where the driving-function is just beginning.

EFFECTOR ORGAN	RECEPTOR FIELD	TEMPERATURE STIMULUS °C	CHANGE IN RECEPTOR SINGLE NEURON FIRING RATE/MINUTE	CALORIC RESPONSE CAL/SEC
SWEATGLANDS	CENTRAL (WARM-DRIVE)	+ 0.1	+ 50	- 20
METABOLISM	CENTRAL (WARM-INHIBITION	+ 0.1	+ 50	- 20
METABOLISM	SKIN (COLD-DRIVE)	+ 4.0	+ 120	+ 20
SWEATGLANDS	SKIN (COLD-INHIBITION)	+ 0.4	+ 12	+ 20